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(71) Applicant *(for all designated States except US)*: **DYNOGEN PHARMACEUTICALS, INC.** [US/US]; 31 St.James Avenue, Suite 905, Boston, MA 02116 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **FRASER, Matthew, Oliver** [US/US]; 408 Gablefield Lane, Apex, NC 27502 (US). **THOR, Karl, Bruce** [US/US]; 109 Draymore Way, Morrisville, NC 27560 (US). **BURGARD, Edward, C.** [US/US]; 215 Cates Farm Road, Chapel Hill, NC 27516 (US). **BRETTMAN, Lee, R.** [US/US]; 183 Greystone Lane, Sudbury, MA 01776 (US). **LANDAU, Steven, B.** [US/US]; 44 Tanglewood Road, Wellesley, MA 02481 (US). **RICCA, Daniel, J.** [US/US]; 5855 Kiger Road, Rougemont, NC 27572 (US).

(74) Agents: **ERGENZINGER, Edward, R.** et al.; Alston & Bird LLP, Bank of America Plaza, 101 South Tryon Street, Suite 4000, Charlotte, NC 28280-4000 (US).

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(54) Title: METHODS FOR TREATING FUNCTIONAL BOWEL DISORDERS USING $\alpha_2\delta$ SUBUNIT CALCIUM CHANNEL MODULATORS WITH SMOOTH MUSCLE MODULATORS

(57) Abstract: A method is provided for using $\alpha_2\delta$ subunit calcium channel modulators or other compounds that interact with the $\alpha_2\delta$ calcium channel subunit in combination with one or more compounds with smooth muscle modulatory effects to treat functional bowel disorders in patients in need of treatment. According to the present invention, $\alpha_2\delta$ subunit calcium channel modulators include GABA analogs including gabapentin and pregabalin, fused bicyclic or tricyclic amino acid analogs of gabapentin, and amino acid compounds. Compounds with smooth muscle modulatory effects include antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

[received by the International Bureau on 10 November2004 (10.11.04); original claims 1-36 are replaced by amended claims 1-42 (8 pages)]

What is claimed is:

1. A method for treating a functional bowel disorder, which comprises administering to an individual in need thereof a therapeutically effective amount of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator, wherein said smooth muscle modulator is selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist, a spasmolytic, a neurokinin receptor antagonist, a bradykinin receptor antagonist, and a nitric oxide donor.

2. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is a GABA analog.

3. The method of claim 2, wherein said GABA analog is selected from the group consisting of:

a. gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof; and

b. pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

4. The method of claim 1, wherein said smooth muscle modulator is an antimuscarinic.

5. The method of claim 4, wherein said antimuscarinic is selected from the group consisting of:

a. oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

b. tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

c. propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof; and

d. solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

Replacement Sheet

6. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, and wherein said antimuscarinic is oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

7. The method of claim 1, wherein said functional bowel disorder is irritable bowel syndrome.

8. The method of claim 1, wherein said functional bowel disorder is constipation.

9. The method of claim 1, wherein said functional bowel disorder is diarrhea.

10. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are administered orally, transmucosally, sublingually, buccally, intranasally, transurethrally, rectally, by inhalation, topically, transdermally, parenterally, intrathecally, vaginally, or perivaginally.

11. The method of claim 1, wherein at least one detrimental side effect associated with single administration of said $\alpha_2\delta$ subunit calcium channel modulator or single administration of said smooth muscle modulator is lessened.

12. The method of claim 1 wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are contained within a single pharmaceutical formulation.

13. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are contained within separate pharmaceutical formulations.

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14. The method of claim 13, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are administered concurrently.

15. The method of claim 13, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are administered sequentially.

16. A pharmaceutical composition comprising an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator, wherein said smooth muscle modulator is selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist, and a bradykinin receptor antagonist, and wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are in amounts sufficient to treat a functional bowel disorder.

17. The pharmaceutical composition of claim 16, wherein said $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof; and

b. pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

18. The pharmaceutical composition of claim 16, wherein said smooth muscle modulator is an antimuscarinic.

19. The pharmaceutical composition of claim 18, wherein said antimuscarinic is selected from the group consisting of:

a. oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

b. tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

c. propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof; and

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d. solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

20. A pharmaceutical composition comprising an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator, wherein said smooth muscle modulator is selected from the group consisting of a spasmolytic, a neurokinin receptor antagonist, and a nitric oxide donor, and wherein said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator are in amounts sufficient to treat a non-painful symptom of a functional bowel disorder.

21. A pharmaceutical composition comprising gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said gabapentin and said oxybutynin are in amounts sufficient to treat a functional bowel disorder.

22. The pharmaceutical composition of claim 21 wherein said gabapentin is present in an amount from about 50 mg to about 2400 mg, and wherein said oxybutynin is present in an amount equal to or less than about 5 mg.

23. The pharmaceutical composition of claim 22 wherein said gabapentin is in an amount of about 200 mg.

24. The pharmaceutical composition of claim 22 wherein said oxybutynin is in an amount of about 2.5 mg.

25. The pharmaceutical composition of claim 22 wherein said second component is in an amount of about 1.25 mg.

26. A pharmaceutical composition comprising pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a

pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said pregabalin and said oxybutynin are in amounts sufficient to treat a functional bowel disorder.

27. A pharmaceutical composition for the treatment of a functional bowel disorder, comprising gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said gabapentin and said oxybutynin are present in a ratio from about 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively, based on a fraction of their respective ED_{50} values.

28. A combination for the treatment of a functional bowel disorder, comprising gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, in combination with oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, wherein said gabapentin and said oxybutynin are in a weight/weight ratio of from 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively.

29. A packaged kit for a patient to use in the treatment of a functional bowel disorder, comprising:

a. an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator;

b. a container housing said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator; and

c. instructions for carrying out drug administration of said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator in a manner effective to treat a functional bowel disorder;

wherein said smooth muscle modulator is selected from the group consisting of an antimuscarinic, a β3 adrenergic agonist, and a bradykinin receptor antagonist.

30. The packaged kit of claim 29 wherein said $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof; and

b. pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

31. The packaged kit of claim 29 wherein said antimuscarinic is selected from the group consisting of:

a. oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

b. tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

c. propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof; and

d. solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

32. The packaged kit of claim 29 wherein said $\alpha_2\delta$ subunit calcium channel modulator is gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, and wherein said antimuscarinic is oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

33. The packaged kit of claim 32, wherein said gabapentin and said oxybutynin are contained in a single pharmaceutical formulation.

34. The packaged kit of claim 32 wherein said gabapentin and said oxybutynin are contained in separate pharmaceutical formulations.

35. The packaged kit of claim 34 wherein said instructions include directions for carrying out drug administration of said gabapentin and said oxybutynin sequentially or concurrently.

36. A packaged kit for a patient to use in the treatment of a non-painful symptom of a functional bowel disorder, comprising:

a. an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator;

b. a container housing said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator; and

c. instructions for carrying out drug administration of said $\alpha_2\delta$ subunit calcium channel modulator and said smooth muscle modulator in a manner effective to treat a functional bowel disorder;

wherein said smooth muscle modulator is selected from the group consisting of a spasmolytic, a neurokinin receptor antagonist, and a nitric oxide donor.

37. The packaged kit of claim 36 wherein said $\alpha_2\delta$ subunit calcium channel modulator is selected from the group consisting of:

a. gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof; and

b. pregabalin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

38. The packaged kit of claim 36 wherein said antimuscarinic is selected from the group consisting of:

a. oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

b. tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof;

c. propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof; and

d. solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

39. The packaged kit of claim 36 wherein said $\alpha_2\delta$ subunit calcium channel modulator is gabapentin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof, and wherein said antimuscarinic is oxybutynin or a pharmaceutically acceptable salt, enantiomer, analog, ester, amide, prodrug, metabolite, or derivative thereof.

40. The packaged kit of claim 39, wherein said gabapentin and said oxybutynin are contained in a single pharmaceutical formulation.

41. The packaged kit of claim 39 wherein said gabapentin and said oxybutynin are contained in separate pharmaceutical formulations.

42. The packaged kit of claim 41 wherein said instructions include directions for carrying out drug administration of said gabapentin and said oxybutynin sequentially or concurrently.